2/10/07

PRIORITY

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? b 155, 5
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           $0.00    0.071 DialUnits File410
     $0.00  Estimated cost File410
     $0.01  TELNET
     $0.01  Estimated cost this search
     $0.01  Estimated total session cost   0.222 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-2002/Dec W3
*File 155: Updating of completed records has resumed.See Help News155.
Alert feature enhanced with customized scheduling. See HELP ALERT.
  File   5:Biosis Previews(R)  1969-2002/Dec W5
         (c) 2002 BIOSIS
*File   5: Alert feature enhanced for multiple files, duplicates
removal, customized scheduling. See HELP ALERT.

      Set  Items  Description
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? s rad51
      S1    1357  RAD51
? s s1 and chemotherapeutic
           1357  S1
          27928  CHEMOTHERAPEUTIC
      S2       3  S1 AND CHEMOTHERAPEUTIC
? rd
...completed examining records
      S3       2  RD (unique items)
? t s3/3,ab/all

 3/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10839241   20379029   PMID: 10843985
  The breast cancer susceptibility gene BRCA1 is required for subnuclear
assembly of Rad51 and survival following treatment with the DNA
cross-linking agent cisplatin.
  Bhattacharyya A; Ear U S; Koller B H; Weichselbaum R R; Bishop D K
  Department of Radiation & Cellular Oncology, University of Chicago,
Chicago, Illinois 60637, USA.
  Journal of biological chemistry (UNITED STATES)  Aug 4 2000,  275  (31)
 p23899-903,  ISSN 0021-9258  Journal Code: 2985121R
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  Mutations in breast cancer tumor susceptibility genes, BRCA1 and BRCA2,
predispose women to early onset breast cancer and other malignancies. The
Brca genes are involved in multiple cellular processes in response to DNA
damage including checkpoint activation, gene transcription, and DNA repair.
Biochemical interaction with the recombinational repair protein Rad51
(Scully, R., Chen, J., Ochs, R. L., Keegan, K., Hoekstra, M., Feunteun, J.,
and Livingston, D. M. (1997) Cell 90, 425-435), as well as genetic evidence
(Moynahan, M. E., Chiu, J. W., Koller, B. H., and Jasin, M. (1999) Mol.
Cell 4, 511-518 and Snouwaert, J. N., Gowen, L. C., Latour, A. M., Mohn, A.
R., Xiao, A., DiBiase, L., and Koller, B. H. (1999) Oncogene 18,
7900-7907), demonstrates that Brca1 is involved in recombinational repair
of DNA double strand breaks. Using isogenic Brca1(+/+) and brca1(-/-) mouse
embryonic stem (ES) cell lines, we investigated the role of Brca1 in the
cellular response to two different categories of DNA damage: x-ray induced
damage and cross-linking damage caused by the chemotherapeutic agent,
cisplatinum. Immunoflourescence studies with normal and brca1(-/-) mutant
mouse ES cell lines indicate that Brca1 promotes assembly of subnuclear
Rad51 foci following both types of DNA damage. These foci are likely
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to be oligomeric complexes of **Rad51** engaged in repair of DNA lesions or in processes that allow cells to tolerate such lesions during DNA replication. Clonogenic assays show that brca1(-/-) mutants are 5-fold more sensitive to cisplatinum compared with wild-type cells. Our studies suggest that Brca1 contributes to damage repair and/or tolerance by promoting assembly of **Rad51**. This function appears to be shared with Brca2.

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 3/3,AB/2      (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

13514123   BIOSIS NO.: 200200142944
Mutation in BRCA2 reduces use of error-free DNA repair by sister chromatid
  recombination and stimulates error-prone DNA repair by homology directed
  single-strand annealing.
AUTHOR: Tutt A N(a); Bertwistle D; Valentine J; Gabriel A; Swift S; Ross G
  M; Griffin C; Thacker J; Ashworth A
AUTHOR ADDRESS: (a)Breakthrough Toby Robins Breast Cancer Research Centre,
  Institute of Cancer Research, London**UK
JOURNAL: Breast Cancer Research and Treatment  69 (3):p255 October, 2001
MEDIUM: print
CONFERENCE/MEETING: 24th Annual San Antonio Breast Cancer Symposium  San
Antonio, Texas, USA  December 10-13, 2001
ISSN: 0167-6806
RECORD TYPE: Citation
LANGUAGE: English
2001
? ds

Set      Items   Description
S1        1357   RAD51
S2           3   S1 AND CHEMOTHERAPEUTIC
S3           2   RD (unique items)
? s s1 and antisense
             1357  S1
            36304  ANTISENSE
      S4       18  S1 AND ANTISENSE
? rd
...completed examining records
      S5       12  RD (unique items)
? t s5/3,ab/all

 5/3,AB/1      (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13105761   21659790   PMID: 11801733
   Formation of higher-order nuclear Rad51 structures is functionally
linked to p21 expression and protection from DNA damage-induced apoptosis.
  Raderschall  Elke;  Bazarov  Alex;  Cao Jiangping;  Lurz  Rudi;  Smith Avril;
Mann  Wolfgang;  Ropers  Hans-Hilger;  Sedivy  John  M;  Golub Efim I;  Fritz
Eberhard;  Haaf Thomas
  Max Planck Institute of Molecular Genetics, 14195 Berlin, Germany.
  Journal of cell science (England)  Jan 1 2002,  115  (Pt 1)  p153-64,
ISSN 0021-9533   Journal Code: 0052457
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  After  exposure  of  mammalian  cells  to  DNA  damage,  the  endogenous
Rad51  recombination  protein  is  concentrated  in multiple discrete
foci,  which  are  thought to represent nuclear domains for recombinational
DNA  repair.  Overexpressed  Rad51  protein forms foci and higher-order
nuclear structures, even in the absence of DNA damage, in cells that do not
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undergo DNA replication synthesis. This correlates with increased expression of the cyclin-dependent kinase (Cdk) inhibitor p21. Following DNA damage, constitutively **Rad51**-overexpressing cells show reduced numbers of DNA breaks and chromatid-type chromosome aberrations and a greater resistance to apoptosis. In contrast, **Rad51 antisense** inhibition reduces p21 protein levels and sensitizes cells to etoposide treatment. Downregulation of p21 inhibits **Rad51** foci formation in both normal and **Rad51**-overexpressing cells. Collectively, our results show that **Rad51** expression, **Rad51** foci formation and p21 expression are interrelated, suggesting a functional link between mammalian **Rad51** protein and p21-mediated cell cycle regulation. This mechanism may contribute to a highly effective recombinational DNA repair in cell cycle-arrested cells and protection against DNA damage-induced apoptosis.

5/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12869845 21626115 PMID: 11754170
Expression of base excision, mismatch, and recombination repair genes in the organogenesis-stage rat conceptus and effects of exposure to a genotoxic teratogen, 4-hydroperoxycyclophosphamide.
Vinson R K; Hales B F
Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada, H3G 1Y6.
Teratology (United States) Dec 2001, 64 (6) p283-91, ISSN 0040-3709 Journal Code: 0153257
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: DNA repair capability may influence the outcome of genotoxic teratogen exposure. The goals of this study were to assess the expression of base excision repair (BER), mismatch repair (MMR), and recombination repair (RCR) genes in the mid-organogenesis rat conceptus and to determine the effects on expression of exposure to the genotoxic teratogen, 4-hydroperoxycyclophosphamide (4-OOHCPA). METHODS: The expression of 17 BER, MMR, and RCR genes was examined in gestational day (GD) 10-12 rat conceptuses using the **antisense** RNA (aRNA) technique. Embryos were cultured with 10 microM 4-OOHCPA to examine effects on gene expression. RESULTS: Yolk sacs and embryos had similar gene expression patterns for all three DNA repair pathways from GD10-12. Transcripts for APNG, PMS1, and RAD54 were present at high concentrations in both tissues. The remainder of the genes were expressed at low levels in yolk sac, with a few not detected on GD10 and 11. In the embryo, transcripts for most genes were low on GD10 and 11; several increased by GD12. After exposure to 4-OOHCPA for 24 hr, XRCC1 and RAD57 expression decreased in yolk sac, whereas only **RAD51** transcripts decreased in the embryo. By 44 hr, transcripts for all BER genes decreased in yolk sac; in the embryo, most BER, MMR, and RCR genes decreased, many below the level of detection. CONCLUSIONS: The expression of DNA repair genes in the mid-organogenesis rat conceptus is varied and subject to down-regulation by 4-OOHCPA. DNA repair gene expression may determine the consequences of genotoxicant exposure during development.

5/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09805408 98238634 PMID: 9571148
In vitro and in vivo potentiation of radiosensitivity of malignant gliomas by **antisense** inhibition of the **RAD51** gene.
Ohnishi T; Taki T; Hiraga S; Arita N; Morita T
Department of Neurosurgery, Osaka University Medical School, Japan.

ohnishi@nsurg.med.osaka-u.ac.jp
Biochemical and biophysical research communications (UNITED STATES) Apr 17 1998, 245 (2) p319-24, ISSN 0006-291X Journal Code: 0372516
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The mammalian **RAD51** gene is a homologue of the yeast **RAD51** and E. coli RecA genes, which are related to the repair of DNA double-strand breaks and are also involved in recombination repair and various SOS responses to DNA damage by gamma-irradiation and alkylating reagents. In this study, we investigated both in vitro and in vivo whether inhibition of the **RAD51** gene by **antisense** oligonucleotides (ODNs) enhances the radiosensitivity of mouse malignant gliomas. A volume of 100 nM of **RAD51 antisense** ODNs inhibited the level of mRNA by more than 95% and reduced the protein expression by about 70%. Treatment of mouse 203G glioma cells with 100 nM of **RAD51 antisense** ODNs significantly enhanced the radiation-induced cell kill compared to control cells, and cells treated with sense or scrambled ODNs. When the glioma cells were implanted in the cisterna magna of mice followed by treatment with **RAD51 antisense** ODNs, the survival time of the mice was markedly prolonged compared to that of the untreated group ($p < 0.001$, logrank test). In addition, the combination of **antisense** ODNs and irradiation extended the survival time of the glioma-bearing mice much longer than could be achieved with radiation alone ($p < 0.0001$, logrank test). These results suggest that inhibition of **RAD51** can be expected to serve as a novel potentiator for radiation therapy in malignant gliomas by inhibiting DNA double-strand break repair.

5/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09740240 98175545 PMID: 9515792
BRCA1 up-regulation is associated with repair-mediated resistance to cis-diamminedichloroplatinum(II).
Husain A; He G; Venkatraman E S; Spriggs D R
Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.
Cancer research (UNITED STATES) Mar 15 1998, 58 (6) p1120-3, ISSN 0008-5472 Journal Code: 2984705R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

We sought to identify novel genes associated with cis-diamminedichloroplatinum(II) (CDDP) resistance, and by differential display analysis, we found that the human breast and ovarian cancer susceptibility gene BRCA1 was overexpressed in CDDP-resistant MCF-7 cells. A recent report that BRCA1 and human **Rad51** colocalize in S-phase cells suggests a role for BRCA1 in DNA damage repair. We hypothesized that BRCA1 plays a role in DNA damage repair-mediated CDDP resistance. In CCDP-resistant variants of breast and ovarian carcinoma cell lines, MCF-7 CDDP/R and SKOV-3 CDDP/R, we found increased levels of BRCA1 protein, and we determined that the SKOV-3 CDDP/R cell line is significantly more proficient at DNA damage repair. **Antisense** inhibition of BRCA1 in this cell line resulted in an increased sensitivity to CDDP, a decreased proficiency of DNA repair, and an enhanced rate of apoptosis. These data support the hypothesis that BRCA1 is a gene involved in DNA damage repair.

5/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09620461 98038784 PMID: 9372947
Elevated recombination in immortal human cells is mediated by HsRAD51 recombinase.
Xia S J; Shammas M A; Shmookler Reis R J
Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock 72205, USA.
Molecular and cellular biology (UNITED STATES) Dec 1997, 17 (12) p7151-8, ISSN 0270-7306 Journal Code: 8109087
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Normal diploid cells have a limited replicative potential in culture, with progressively increasing interdivision time. Rarely, cell lines arise which can divide indefinitely; like tumor cells, such "immortal" lines display frequent chromosomal aberrations which may reflect high rates of recombination. Recombination frequencies within a plasmid substrate were 3.5-fold higher in nine immortal human cell lines than in six untransformed cell strains. Expression of HsRAD51, a human homolog of the yeast **RAD51** and Escherichia coli recA recombinase genes, was 4.5-fold higher in immortal cell lines than in mortal cells. Stable transformation of human fibroblasts with simian virus 40 large T antigen prior to cell immortalization increased both chromosomal recombination and the level of HsRAD51 transcripts by two- to fivefold. T-antigen induction of recombination was efficiently blocked by introduction of HsRAD51 **antisense** (but not control) oligonucleotides spanning the initiation codon, implying that HsRAD51 expression mediates augmented recombination. Since p53 binds and inactivates HsRAD51, T-antigen-p53 association may block such inactivation and liberate HsRAD51. Upregulation of HsRAD51 transcripts in T-antigen-transformed and other immortal cells suggests that recombinase activation can also occur at the RNA level and may facilitate cell transformation to immortality.

5/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08903269 96264658 PMID: 8670299
Antisense inhibition of the **RAD51** enhances radiosensitivity.
Taki T; Ohnishi T; Yamamoto A; Hiraga S; Arita N; Izumoto S; Hayakawa T; Morita T
Department of Neurosurgery, Osaka University Medical School, Japan.
Biochemical and biophysical research communications (UNITED STATES) Jun 14 1996, 223 (2) p434-8, ISSN 0006-291X Journal Code: 0372516
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The mammalian **RAD51** gene is a homologue of the yeast **RAD51** and E. coli RecA genes, which are involved in recombination and DNA repair. We examined the role of **RAD51** protein in mouse cells using **RAD51** **antisense** phosphorothioate oligonucleotides (ODNs). The extraluminal delivery of 50 nM or 100 nM of **antisense** ODNs with lipofection to mouse cells resulted 90% suppression of **RAD51** protein expression. The **antisense** ODNs significantly inhibited the cell growth and the treated cells became more sensitive to gamma-irradiation than the control groups. These results indicate mouse **RAD51** plays an essential role in cell proliferation and radioresistant activity.

5/3,AB/7 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13821672 BIOSIS NO.: 200200450493
Chk1 signaling pathways that mediated G2M checkpoint in relation to the cellular resistance to the novel topoisomerase I poison BNP1350.
AUTHOR: Yin Ming-biao; Hapke Gunnar; Wu Jiaxi; Azrak Rami G; Frank Cheryl; Wrzosek Carol; Rustum Youcef M(a)
AUTHOR ADDRESS: (a)Department of Pharmacology and Therapeutics, Grace Cancer Drug Center, Roswell Park Cancer Institute, Buffalo, NY, 14263** USA E-Mail: youcef.rustum@roswellpark.org
JOURNAL: Biochemical and Biophysical Research Communications 295 (2):p 435-444 July 12, 2002
MEDIUM: print
ISSN: 0006-291X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A novel karenitecin, BNP1350, is a topoisomerase I-targeting anticancer agent with significant antitumor activity in vitro and in vivo. A BNP1350-resistant human head and neck carcinoma A253 cell line, denoted A253/BNPR, was developed. The A253/BNPR cell line was approximately 9-fold resistant to BNP1350 and 4-fold cross-resistant to another topoisomerase I inhibitor SN-38, the active metabolite of irinotecan. After drug treatment with equimolar concentrations of BNP1350 (0.7 muM) for 2 h, activation of the DNA double-strand break repair protein complexes was similar in the two cell lines, suggesting that DNA dsb repair is not attributable to resistance to BNP1350 in the A253/BNPR cells. Cell cycle analysis indicates that the A253 cell line accumulated primarily in S phase, but G2 phase accumulation was observed in the A253/BNPR cell line at 48 h after drug removal. Elevated chk1 phosphorylation at Ser345 following DNA damage induced by BNP1350 was accompanied by G2 accumulation in the A253/BNPR cell line, while exposure to equimolar concentrations of BNP1350 (0.7 muM) induced S-phase arrest and no increased phosphorylation of chk1 at Ser345 in the A253 cell line. Under the same conditions, increased chk1 activity was observed in the A253/BNPR cell line, but not in the A253 cell line. Moreover, stimulated binding of 14-3-3 proteins to chk1 was observed in BNP1350-treated A253/BNPR cells. To confirm relationship between chk1 expression/phosphorylation and drug resistance to topo I poisons, we examined the effects of chk1 or chk2 **antisense** oligonucleotides on the cellular growth inhibition. Chk1 **antisense** oligonucleotide can sensitize the A253/BNPR cells to killing by topo I inhibitor BNP1350, but no significant sensitization of BNP1350-induced growth inhibition was observed in the drug-sensitive cell line. Chk2 **antisense** oligonucleotide has only a small sensitization effect on BNP1350-induced growth inhibition in both cell lines. The data indicate that the chk1 signaling pathways that mediate cell cycle checkpoint are associated with cellular resistance to BNP1350 in the A253/BNPR cell line.

2002

5/3,AB/8 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13780469 BIOSIS NO.: 200200409290
Rad51 inhibitors sensitize human tumor cells to DNA damaging treatment with doxorubicin or cisplatin.
AUTHOR: Vallerga Anne K(a); Yang Jerry(a); Reddy Guru(a); Zarling David A (a)
AUTHOR ADDRESS: (a)Pangene Corporation, Fremont, CA**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 43p795 March, 2002
MEDIUM: print

CONFERENCE/MEETING: 93rd Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 06-10, 2002
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
2002

5/3,AB/9 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13660030 BIOSIS NO.: 200200288851
The transcriptional inhibition of DNA repair protein **Rad51** enhances radiosensitivity in prostate cancer cells.
AUTHOR: Nishimura H(a); Sasaki R(a); Soejima T(a); Ejima Y(a); Yoden E(a); Shirakawa T; Ota Y(a); Matsumoto A; Sugimura K(a)
AUTHOR ADDRESS: (a)Radiology, Kobe University, Kobe**Japan
JOURNAL: European Journal of Cancer 37 (Supplement 6):pS143 October, 2001
MEDIUM: print
CONFERENCE/MEETING: 11th European Cancer Conference Lisbon, Portugal October 21-25, 2001
ISSN: 0959-8049
RECORD TYPE: Citation
LANGUAGE: English
2001

5/3,AB/10 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13647466 BIOSIS NO.: 200200276287
The transcriptional inhibition of DNA repair protein **Rad51** enhances radiosensitivity in prostate cancer cells.
AUTHOR: Sasaki R(a); Nishimura H(a); Soejima T(a); Ejima Y(a); Yoden E(a); Shirakawa T; Gotoh A; Ota Y(a); Matsumoto A; Sugimura K(a)
AUTHOR ADDRESS: (a)Radiology, Kobe University School of Medicine, Kobe** Japan
JOURNAL: International Journal of Radiation Oncology Biology Physics 51 (3 Supplement 1):p56-57 2001
MEDIUM: print
CONFERENCE/MEETING: 43rd Annual Meeting of the American Society for Therapeutic Radiology and Oncology San Francisco, CA, USA November 04-08, 2001
ISSN: 0360-3016
RECORD TYPE: Citation
LANGUAGE: English
2001

5/3,AB/11 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13115199 BIOSIS NO.: 200100322348
Oncogenic tyrosine kinases derived from chromosomal translocations induce common mechanisms of drug resistance: Overexpression of **RAD51** and G2/M arrest.
AUTHOR: Slupianek A(a); Hoser G; Fishel R; Skorski T
AUTHOR ADDRESS: (a)Temple University, Center for Biotechnology, Thomas Jefferson University, Kimmel Cancer Center, Philadelphia, PA**USA
JOURNAL: Blood 96 (11 Part 1):p825a November 16, 2000
MEDIUM: print

CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000
SPONSOR: American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Oncogenic tyrosine kinases (OTKs) such as BCR/ABL, TEL/ABL, TEL/JAK2, TEL/PDGFR and NPM/ALK arose from the chromosomal translocations induce acute and chronic myelogenous leukemias or non-Hodgkin's lymphoma. Hematopoietic cell lines transformed by these OTKs are resistant to DNA damaging drugs such as cisplatin and mitomycin. Treatment with one of these drugs induce transient G2/M arrest in cells transformed by OTKs, but not in normal cells. G2/M arrest appears to be essential for drug resistance in the former cells. In addition, OTK-transformed cells display elevated levels of **RAD51**, a protein involved in reparation of drug-induced DNA lesions. **RAD51** is a member of conserved family of eukaryotic proteins related to Escherichia coli RecA protein, which plays a central role in prokaryotic response to DNA damage. Both, RecA and **RAD51** promote homology-dependent repair of double strand breaks (DSBs), probably the most disruptive type of lesion in DNA after exposure to DNA-damaging agents. If left unrepaired, DSBs lead to broken chromosomes and cell death. OTKs-induced elevation of **RAD51** expression is probably due to the STAT5-dependent transactivation of **RAD51** promoter. Using the in vivo DSBs repair model in which DSBs are induced in the green fluorescent protein (GFP) sequence and their reparation is assessed by the appearance of GFP+ cells, we found that **RAD51** is responsible for enhanced DSBs repair in OTKs-transformed cells. Downregulation of **RAD51** expression by the **antisense** cDNA reduced almost completely drug resistance in the transformed cells. Since **RAD51**-dependent DSBs repair occurs usually in the late S phase and/or early G2/M phase we postulate that elevated expression of **RAD51** in combination with G2/M arrest is responsible for more efficient repair of drug-induced lethal DNA lesions in OTKs-transformed cells in comparison to normal cells.

2000

5/3,AB/12 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13105365 BIOSIS NO.: 200100312514
Functional link of BCR/ABL oncogenic tyrosine kinase and **RAD51** double strand break repair protein in DNA damage response.
AUTHOR: Slupianek A(a); Tombline G; Schmutte C; Nieborowska-Skorska M; Malecki M; Fishel R; Skorski T
AUTHOR ADDRESS: (a)Center for Biotechnology, Temple University, Philadelphia, PA**USA
JOURNAL: Blood 96 (11 Part 1):p509a November 16, 2000
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000
SPONSOR: American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Double-strand breaks (DSBs), probably the most disruptive type of lesion in DNA, may arise after exposure to DNA-damaging agents. If left unrepaired, DSBs lead to broken chromosomes and cell death. Philadelphia

chromosome-positive (Ph1) leukemias expressing BCR/ABL oncogenic tyrosine kinases are usually resistant to DNA damaging agents (cytostatics, radiation) inducing DSBs. Using representational differences analysis (RDA) followed by Northern blotting and Western blotting we found that BCR/ABL kinase induces overexpression of **RAD51** in hematopoietic cell lines and in chronic myelogenous leukemia (CML) cells. **RAD51** is a member of conserved family of eukaryotic proteins related to Escherichia coli RecA protein, which plays a central role in prokaryotic response to DNA damage. Both, RecA and **RAD51** promote homology-dependent repair of DSBs. BCR/ABL-induced elevation of **RAD51** expression is due to the STAT5-mediated transactivation of **RAD51** promoter and the prevention of **RAD51** cleavage by inhibition of caspase-3. BCR/ABL is in complex with **RAD51** and induces its phosphorylation on Y315, which increases **RAD51** cytoplasmic-nuclear shuttling and assembly on DNA lesions (DSBs). Using the in vivo DSBs repair model in which DSBs are induced in the green fluorescent protein (GFP) sequence and their reparation is assessed by the appearance of GFP+ cells, we found that **RAD51** is responsible for enhanced DSBs repair in BCR/ABL-transformed cells. Inhibition of **RAD51** expression and/or function by the **antisense** cDNA or the Y315F mutant reduced almost completely drug resistance in BCR/ABL-transformed cells. Incubation of BCR/ABL-positive cells with the ABL kinase inhibitor STI571 caused downregulation of expression of **RAD51** and abrogated drug resistance. Expression of exogenous **RAD51** elevated the total amount of **RAD51** protein and partially rescued drug resistance in these cells. In contrast to drug-induced apoptosis, modulation of **RAD51** expression did not affect the susceptibility of normal and BCR/ABL-transformed cells to apoptosis induced by growth factor withdrawal. Moreover, **RAD51** does not seem to be directly involved in regulation of G2/M cell cycle phase, P-glycoprotein or caspase-3, which may be involved in drug resistance. Instead, BCR/ABL-dependent overexpression of **RAD51** is responsible for enhanced reparation of drug-induced lethal DNA lesions (DSBs), which decrease activation/accumulation of the "DNA damage sensor" p73 and reduce the pro-apoptotic signaling from the nucleus. Thus, BCR/ABL-induced and **RAD51**-mediated DNA repair represents a novel mechanism contributing to drug resistance in Ph1 leukemias.

2000